Innate (and innate-like) lymphoid cells: emerging immune subsets with multiple roles along transplant life

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Abbreviations

ADCC: Antibody dependent cellular cytotoxicity

AMR: Antibody-mediated rejection

APC: Antigen presenting cell

CMV: Cytomegalovirus

DC: Dendritic cell

LTi: Lymphoid tissue inducer

DSA: Donor specific antibody

GVHD: Graft versus host disease

HLA: Human leukocyte antigen

ILC: Innate lymphoid cell

ILLC: Innate-like lymphoid cell

IRI: Ischemia reperfusion injury

LN: Lymph node

MAIT: Mucosal associated invariant T

MHC: Major histocompatibility complex

MICA: MHC-I polypeptide–related sequence A

NK: Natural killer

NKaR: Natural killer activating receptor

NKiR: Natural killer inhibitory receptor

NKT: Natural killer T

PBMC: Peripheral blood mononuclear cell

TCR: T cell receptor

TEC: Tubular epithelial cell

Tfh: T follicular helper

Abstract (207 words)

Transplant immunology is currently largely focused on conventional adaptive immunity, particularly T and B lymphocytes, which have long been considered as the only cells capable of allorecognition. In this vision, except for the initial phase of ischemia/reperfusion, during which the role of innate immune effectors is well established, the latter are largely considered as “passive” players, recruited secondarily to amplify graft destruction processes during rejection. Challenging this prevalent dogma, the recent progresses in basic immunology have unraveled the complexity of the innate immune system and identified different subsets of innate (and innate-like) lymphoid cells. As most of these cells are tissue-resident, they are over-represented among passenger leukocytes. Beyond their role in ischemia/reperfusion, some of these subsets have been shown to be capable of allorecognition and/or of regulating alloreactive adaptive responses, suggesting that these emerging immune players are actively involved in most of the life phases of the grafts and their recipients.

Drawing upon the inventory of the literature, this review synthesizes the current state of knowledge of the role of the different innate (and innate-like) lymphoid cell subsets during ischemia/reperfusion, allorecognition and graft rejection. How these subsets also contribute to graft tolerance and the protection of chronically immunosuppressed patients against infectious and cancerous complications is also examined.

Introduction

According to World Health Organization reports, terminal failure of a vital organ is the first cause of death in industrialized countries, accounting for ~25% of total health expenditures. Solid organ transplantation is the best (often the only) therapeutic option for these patients.

Transplantation procedure however implies exposing the grafts to ischemia/reperfusion, which not only creates damage to the tissues but also represents an immunogenic context[1,2] favorable to allorecognition: the detection by the recipient's adaptive immune system of polymorphic determinants expressed by different individuals of the same species (such as donor-specific Major Histocompatibility Complex (MHC) molecules). Allorecognition in turn results in the generation of immune effectors responsible for graft destruction, a process known as rejection, which represents the first cause of late failure in transplantation[3,4]. To prevent rejection, transplanted patients are treated with immunosuppressive drugs. Because the latter therapies are non-specific, they reduce immunosurveillance efficiency and increase the risk of infections and cancers[5–7].

The prevalent dogma in transplant immunology is that only adaptive immune effectors (T and B lymphocytes equipped with clonal receptors) are capable of allorecognition (through the direct and the indirect pathways)[8–10]. In this vision, innate immune effectors are often overlooked, being only secondarily recruited by allospecific adaptive effectors to amplify graft destruction and accelerate rejection.

Over the last decades considerable progress has been made in deciphering the complexity of the innate immune system, which consists in a myriad of molecular (complement system for instance) but also cellular effectors belonging to both the myeloid and the lymphoid lineages.

Recent works from the Lakkis group have challenged the previous dogma by demonstrating that innate effectors from the myeloid lineage were capable of allorecognition independently of the adaptive immune system[11–13], paving the way for the concept of « innate rejection ».

In the present article, we synthetize published data on the very recently discovered innate (and innate-like) immune effectors from the lymphoid lineage (Figure 1). These cells are of particular interest in the field of transplant immunology because most of them are tissue-resident, and therefore over-represented among passenger leukocytes[14]. Furthermore, beyond their role in ischemia/reperfusion, some of these subsets have been shown to be capable of allorecognition and/or of regulating alloreactive adaptive responses, suggesting that these emerging immune players are actively involved in most of the life phases of the grafts and their recipients.

Innate lymphoid cells, what's in a name?

More than 40 years ago, lymphoid cells that could recognize and kill various tumor cell lines without prior stimulation with cytokines or antigen were identified[15]. These cells, named Natural Killer (NK) cells with respect to their innate properties, were devoid of antigen receptors encoded by somatically rearranged gene segments. This initial discovery was then followed many years later by the characterization of several other immune cell types capable of rapid cytokine production upon stimulation and with typical lymphoid morphology, despite the lack of a B or T cell antigen receptor. Due to their ontological relationships, these cell types were grouped under the name innate lymphoid cells (ILCs). ILCs are now subdivided in three groups corresponding to T cell helper groups in terms of cytokine secretion patterns (Figure 2).

Group 1 ILCs

NK cells

NK cells are defined by co-expression of T-bet and Eomes transcription factors in both mouse and human, whereas other group 1 ILCs (ie ILC1s) only express one either factor[16]. NK cell activation is controlled by a series of inhibitory (NKiR) and activating (NKaR) receptors. NKiR mainly engage major histocompatibility complex (MHC)-I molecules expressed by almost every healthy cell, ensuring tolerance. By contrast, NKaR interact with cellular ligands whose expression is increased upon cell transformation or infection. The relative engagement of NKaR vs NKiR determines NK cell response: activation (cytokine secretion and cytotoxicity) or tolerance[17]. As opposed to T lymphocytes, which require priming from antigen-presenting cells (APCs), NK cells are naturally poised to kill infected or tumor cells. Yet NK cell cytotoxic activity can be enhanced upon stimulation with various cytokines such as IL-2, IL-15, IL-12/IL-18 or IL-21[18].

In both mouse and human, immature NK cells express high levels of the CD94/NKG2A NKiR heterodimer while mature NK cells express a higher frequency of inhibitory KIR (Killer Cell Immunoglobulin-like receptor, human) or Ly49 (mouse) receptors allowing missing-self recognition[19,20]. However, maturation is not sufficient to acquire responsiveness and NK cells need to be educated to be able to gauge MHC-I surface expression[21]. This education process involves continuous engagement and signaling through SHP1 of NKiR by their MHC-I ligands. In the absence of such signals, NK cells are hypo-responsive, unable to reject MHC-I negative cells.

NK cells are the only ILCs known to circulate in the blood at steady state. They are strategically positioned in the lymph nodes (LNs) to rapidly respond to cytokines produced by dendritic cells (DCs) and monocytes upon pathogen infections[22,23]. Many

studies have documented the important role of NK cells in mice infected with various viruses or intracellular pathogens. In humans, a functional redundancy between NK cells and various T cell subsets may compensate for decreased NK cell responses. Yet, patients with selective NK cell deficiencies suffer from recurrent infections, in particular from viruses of the herpes class[24]. Many NKaR expressed by NK cells can recognize some viral determinants[25], which further supports this point.

The various and sophisticated evasion processes selected by many viruses to escape NK cells is also an indirect indication that these cells are important for the control of viral infections[26]. NK cells also contribute to anti-tumor responses. This has been well demonstrated in mouse where multiple studies have documented the impact of NK cell depletion/deficiency on tumor growth. NK cells can directly recognize and kill tumor in vivo, but also provide an essential source of IFNγ to polarize and stimulate T cell responses[27].

ILC1s

ILC1s are Eomes-/T-bet+ in mouse[28,29], but various phenotypes have been described in human, with some cells being Eomes+/T-bet-[16]. ILC1s are tissue-resident and have low cytotoxic activity, but have a strong capacity to produce IFNγ and other inflammatory cytokines in response to cytokine stimulation[28,29].

The role of ILC1s in immunity recently came to light when it was found that mice deficient for the Hobit transcription factor had a relatively specific deficiency in ILC1s[30]. This new model showed that ILC1s responded very early during viral infections to IL-12 produced by DCs, by producing large amounts of IFNγ[31]. ILC1s can also expand and produce cytokines during infections by intracellular parasites[32]. Moreover, recent analyses using Hobit-deficient mice have demonstrated that ILC1s and NK cells cooperate in anti-tumor responses[33].

Group 2 ILCs

Group 2 ILCs only comprise ILC2s that were initially discovered as an important source of type 2 cytokines IL-5 and IL-13 during parasitic infections[34–36]. ILC2s are tissue resident and widely distributed, but particularly abundant at mucosal sites (lung and gastro-intestinal tract)[37]. Human ILC2s have been described as well as the high GATA3 expression defining this cell type[38]. ILC2s have the capacity to expand in response to IL-25 and IL-33, upon local or systemic administration of these cytokines or during helminth infections[34–36]. Moreover, despite the fact that tissue residency was considered a hallmark of helper ILCs, ILC2s were found to recirculate in the blood in response to IL-25 or helminth infection[39].

ILC2s are involved in protective immune responses against parasites[34,35]. The cytokines they express activate multiple cell types, leading to parasite destruction or expulsion. Moreover, they can promote tissue remodeling and repair, notably through the production of Amphiregulin, a member of the epithelial growth factor[40]. Finally, they are also involved in pathological immune responses in cases of allergy, and other types of inflammation at mucosal sites such as skin and airways[41]. Moreover, a recent study reported that IL-33-induced activation of ILC2 suppressed NK cell anti-tumor functions through IL-5-induced lung eosinophilia[42].

Group 3 ILCs: LTi and other ILC3s

Group 3 ILC includes three main subsets: lymphoid tissue inducers (LTi), and other “non-LTi” ILC3s, including natural cytotoxicity receptors (NCR)+ and NCR- ILC3. These three subsets depend on the transcription factor RORγt[43] and have the capacity to secrete IL-17A and IL-22[44–46]. ILC3s are particularly enriched in the gastrointestinal tract, and LTi are additionally located in lymphoid organs such as LNs and Peyer’s patches. LTi colonize fetal lymphoid structures and are essential for the development

of secondary lymphoid organs (LNs and Peyer's patches but also lymphoid structures associated with the intestinal mucosa called isolated lymphoid follicles)[43,47,48]. LTi induce lymphoid organogenesis through surface expression of lymphotoxin α1 β2 and interactions with stromal cells[43,47].

Group 3 ILC participate in antimicrobial responses and maintenance of mucosal integrity. ILC3s are indeed the main source of IL-22 in the small intestine. ILC3-derived IL-22 acts directly on epithelial cells and induces the release of antimicrobial peptides[49,50], stimulates antiviral responses against rotavirus by activating IFN-lambda pathways[51] and helps repair and heal the intestinal barrier after inflammation by promoting stem cell proliferation[52]. LTi also produce IL-17A, an important pro-inflammatory mediator for antibacterial and antifungal responses that promotes neutrophil infiltration. IL-17-producing ILC3s have been shown to accumulate in the lamina propria of the colon of mice with bacterial-induced colitis and participate in inflammation[53].

Beyond ILC: “innate-like” lymphoid cells

Innate-like lymphoid cells

Innate-like lymphoid cells bridge innate and adaptive lymphoid cells (Figure 1 & Figure 3).

Subsets of innate-like B cells have been identified (Figure 1), including B1 and marginal zone B cells[54]. They are characterized by semi-invariant (or germ-line-encoded) BCR with limited diversity. Consequently, antibodies generated from B1 cells and MZ B cells are polyreactive and autoreactive, with the capacity to recognize conserved structures across species. Following triggering by TLR agonists or microbial pathogens, innate-like B cells produce a large amount of natural IgM, providing a critical early defense against infections, and IL-10, a key regulatory cytokine that plays

a crucial role in downmodulating immune responses[55]. As evidence of the involvement of innate-like B cells in transplant immunology is scarce, the present review will focus on innate-like T cells (ILTCs).

ILTCs share several characteristics, including: i) expression of a functional T Cell Receptor (TCR) that monitors cell surfaces within tissues and acts as a rapid sensor of dysregulation, ii) generation during early life, iii) response that does not require prior clonal expansion, and iv) response that depends on the integration of TCR, cytokine-dependent signals, costimulation and NK cell receptor signaling, allowing for a large panel of effector responses depending on the context.

Based on the nature of the TCR, ILTCs can be divided in three main types i.e. Natural Killer T cells (NKT), Mucosal Associated Invariant T cells (MAIT) and gamma delta (γδ) T cells. In human, MAIT, NKT and γδ T cells represent 10%, 0.1% and 0.5-20% of circulating T cells, respectively. These proportions are increased among tissue resident T cells, especially in liver and lung for MAIT and NKT, and mucosal tissues for γδ T cells.

ILTCs undergo thymic selection but are not restricted to MHC since they develop normally in β2microglobulin KO mice[56]. The TCR of NKT, MAIT and Vγ9+Vδ2+ T cells is semi-invariant but is highly diverse for the other γδ T cells (owing to RAG-mediated V(D)J recombination).

γδ T cells

Gamma delta T cells are the first T cells to develop in vertebrates. In humans, γδ T cell groups are functionally defined based on their γ and δ TCR chain expression: Vγ9+Vδ2+ T cells are usually opposed to Vδ2-negative γδ T cells.

Vγ9+Vδ2+ T cells sense variations in cellular production of phosphorylated metabolites of the isoprenoid pathway (called phosphoantigens). The most active phosphoantigens

are produced by microorganisms such as Gram-positive bacteria, *Mycobacterium tuberculosis*, *Plasmodium falciparum* and *Toxoplasma gondii*. Less active endogenous phosphoantigens can also accumulate in host cells upon activation or transformation. The recognition of ubiquitous microbial or stress signals by Vγ9+Vδ2+ TCR is reminiscent of the pattern recognition receptors (PRRs) process and is supported by the semi-invariant V-usage of these γδ TCRs. Recent breakthroughs underline the importance of butyrophilins, which bind to phosphoantigens intracellularly[57] and to Vγ9-chain[58,59].

All the other γδ T cells, collectively called Vδ2-negative γδ T cells (mainly expressing the Vδ1 and Vδ3 chains), but to which the Vγ9-Vδ2+ population was recently integrated[60], are considered to recognize a large panel of stress-induced antigens in the context of transformed or infected cells (especially by cytomegalovirus, CMV). Yet, most Vδ2-negative γδ T cell antigens remain to be identified. With a shorter CDR3g and a longer CDR3d carrying diversity the TCR of Vδ2-negative γδ T cells resembles that of immunoglobulins and can therefore recognize conformational and sequential epitopes. Their ability to differentiate health and stress conditions relies on different mechanisms: differential expression of the TCR ligand upon stress, requirement of costimulatory molecules for full activation, conformational changes of the ligand (multi or monomerization), and differential glycosylation. Although the affinity of their TCR is low, Vδ2-negative γδ T cells interact with their cellular targets with high avidity due to the high density of TCR and ligand molecules on cell surfaces. Over the last decades, a plethora of structurally highly diverse TCR ligands have been identified, often restricted to one clone of Vδ2-negative γδ T cell, with no systematic generalization and uncertain physiological relevance[61]. The multiplicity of presumed ligands for Vδ2-

negative γδ T cell cells however illustrate the potentiality of what has been described as "beneficial self-immunogenicity"[62].

MAIT cells

In contrast with mice, MAIT cells are the largest subset of unconventional T cells in human blood and tissue (up to 100 times more than NKTs).

The TCR of MAIT is composed of invariant TCR α chains (Vα7.2Jα33/12/20) paired with a biased repertoire of Vβ chains (Vβ2 or Vβ13) that recognize a limited range of non-peptide ligands (riboflavin) presented by monomorphic MHC-like molecules (MR1)[63,64].

MAIT are CCR7-CD161^{high}CD26^{high} and CD8αα (80%) and constitute a homogeneous population with mixed Th1/Th17 functions and cytotoxic properties (perforin/granzyme), the development of which depends on a microbiota-derived metabolite[65].

NKT cells

In contrast with MAIT, the development of NKT cells is conserved in germ-free mice. However, the transcription factor PLZF (promyelocytic leukemia zinc finger) is important for both MAIT and NKT and governs the acquisition of innate-like characteristics with effector function and memory phenotype in both subsets[66–69].

Although their TCR is specific for glycolipid/phosphoslipid antigens bound to the monomorphic MHC-like molecules CD1[70], NKT cells are highly diverse and distributed into two subgroups:

- Type I NKT or invariant (iNKT), the TCR of which, made of Vα24-Jα18 TCRα chain paired exclusively with Vβ11, is specific for CD1d-restricted α-galactosylceramide glycopeptide (αGalCer);

- Type II NKT cells which are non-invariant and their TCR recognizes CD1-restricted diverse sulfatide and lysophophatidylcholine antigens.

Ischemia reperfusion injuries

The sequence of ischemia/reperfusion which strikes the transplanted organ is a model of violent sterile inflammation. Peri-surgical procedure and each additional hour of ischemia increases the risk of graft failure and mortality[71].

Ischemia/reperfusion injuries (IRI) cause mitochondrial damages due to variation of oxygen access with ATP depletion followed by the release of reactive oxygen species (ROS). The subsequent development of an inflammatory response leads to tissue damage and eventual cell death. Tissue resident ILCs/ILTCs-are pre-armed effectors, prone to sense the danger signals and mount a rapid response to preserve tissue integrity. However, this response may also exacerbate necroinflammation and thereby promote allorecognition[2].

Danger-associated molecular patterns (DAMPs) and ILCs/ILTCs

IRI promotes the release of alarmins (in particular IL-33). IL-33 is a chromatin-associated nuclear cytokine from the IL-1 family which is generated in an inflammatory environment[72]. In a mouse model of kidney transplantation, microvascular endothelial cells produce IL-33 which in turn signals on its receptor ST2 expressed on iNKT cells. This contributes to their recruitment and cytokine production (IFN-γ and IL17), resulting in neutrophil infiltration and activation at the injury site[73,74]. Contrary to their invariant counterparts, NKT may abrogate IRI through the secretion of IL-10[75].

IL-33 may also activate ILC2s. The expansion of ILC2s has a protective effect in mouse glomerulonephritis[76] and promotes tissue repair and metabolic homeostasis in adipose tissue[77]. Protection of IRI by ILC2s is also suggested in kidney and may be mediated by IL-25[78].

Other ILCs were reported to protect tissue from acute injury with mechanisms which could also intervene in IRI: ILC1s protect mice from acute liver injury after carbon tetrachloride injection via IFNγ secretion and upregulation of Bcl-xl expression in hepatocytes[79]. ILC3s are potent producers of IL-22 after intestinal injury and target intestinal stem cell expansion and then intestinal regeneration through STAT3 phosphorylation[80].

In general, inflammation seems to induce dynamic changes in the balance of ILCs and ILTCs in tissue and in peripheral blood. Recently, ILC1s were reported to be significantly increased in the peripheral blood of patients with acute ST-segment elevation myocardial infarction and associated with poor outcome[81]. If ILCs/ILTCs are sometimes associated with protection, they can also take part in an amplification loop of cell death and inflammation. In this regard, high-mobility group box-1 (HMGB1), which is involved in IRI in liver[82] and in kidney[83] has been shown to exacerbate experimental mouse colitis through ILC3s[84].

NK cells, ILC1s and IRI

NK cells promote apoptosis of stressed tubular epithelial cells (TEC)[85].

IRI promote NK cell recruitment by TLR2 engagement[86,87] or by reverse signaling of CD137L (also known as 4-1BBL and TNFSF9)[88] with the subsequent production of chemokines and maybe a special role for osteopontin[89]. However peripheral NK cells might not be the most important in ischemic kidney injury. In mouse, ILC1s display a distinct phenotype. Compared with circulating NK cells, ILC1s have reduced expression of asialo-GM1 (AsGM1) and anti AsGM1 antibody treatment therefore does not affect ILC1s. Because anti-AsGM1 antibody fails to protect against IRI, while anti-NK1.1 antibody does, Victorino et al[90] concluded that ILC1s rather than NK cells might have the prominent role in kidney IRI. Of note, kidney MAIT cells, which get activated

in the presence of TECs cultured under hypoxic conditions and display upregulated expression of CD69 and cytotoxic molecules[91], might also be involved in IRI-induced kidney injury. This data suggests a potential role for passenger leukocytes (i.e. originating from the donor, ILC1s and MAIT) in IRI. However, circulating recipient NK cells could also take part in this phenomenon.

The reason why NK cells get activated by ischemia/reperfusion could rely on their ability to sense the discontinuity of self-antigens[92]. Human leukocyte antigen (HLA)-E is a non-classical MHC-I molecule with a limited polymorphism which presents a restricted set of nonameric peptides, mainly derived from the leader sequences of classical HLA-I proteins[93]. HLA-E is a major ligand for the NKiR CD94/NKG2A[94]. During cellular stress, an increased proportion of HLA-E molecules may bind the heat shock protein 60 signal peptide, leading to peptide interference that would gradually uncouple CD94/NKG2A inhibitory recognition and provide a mechanism for NK cells to detect stressed cells[95]. IRI also promote MHC-I polypeptide–related sequence A (MICA) expression during acute myocardial infarction[96] or in TEC through HIF as a response to hypoxia/reoxygenation[97]. NKG2D is the receptor for the stress-inducible MICA and its engagement activates a cytolytic response in NK cells[98]. Cytotoxicity resulting from NK cell activation through NKG2D may lead to allograft damage as already reported in the development of murine bronchiolitis obliterans[99]. Interestingly, MAIT[100], iNKT[101], and γδ T cells[98] also express NKG2D and could take part in this pathological process.

γδ T cells and IRI

Annexin A2 is unique among annexins in that it possesses redox sensitive cysteine(s)[102]. Cells exposed to ROS upregulate the expression of surface Annexin A2, which is a ligand for a Vγ8Vδ3 TCR[103]. Annexin A2 can stimulate the proliferation

of a fraction of (Vδ2-) T cells within peripheral blood mononuclear cells (PBMCs), and other annexin A2-specific γδ T-cell clones could be derived from PBMCs[103]. The Vγ4Vδ5 TCR mediates recognition of broadly stressed human cells by engaging a stress-regulated self-antigen (Endothelial protein C receptor) co-expressed with stress-induced costimulatory ligands[104]. β2-microglobulin-free HLA-I heavy chain (FHC) or open conformer can be recognized as a stress antigen by Vγ9Vδ3 T cells[105]. MIC-A/B are also directly recognized by the TCR of tumor-infiltrating γδ T cells[106].

Finally, Guerville et al have demonstrated that TCR signaling sensitizes γδ T cells to inflammatory mediators, and in particular IL-18, the receptor of which is upregulated at the cell surface after TCR engagement. Moreover, IL-18 secretion, which follows the caspase-1 inflammasome activation in stressed cells, could be a unified signal to alert γδ T cells[107].

A mouse model of ischemic brain injury confirms the implication of IL-17 production by γδ T cells in the delayed phase of ischemia-reperfusion[108], with the implication of peroxiredoxin family proteins as key initiators[109]. Commensal microbiota affects ischemic stroke by regulating intestinal γδ T cells[110]. This implication of γδ was found in other models of renal IRI[111].

At present, there is no data that would allow the responsibility of passenger γδ versus recipient's γδ T cells to be apportioned in the IRI mechanisms. It is conceivable that both populations are involved, the first one inside the graft, the second one at the blood/graft endothelium interface.

Allorecognition

Allorecognition designates the recognition by the recipient's adaptive immune system of donor-specific alloantigens. Several pathways of allorecognition have been

evidenced[8–10]. The direct pathway involves the recognition of intact allogeneic HLA molecules on the surface of donor passenger APCs. The semi-direct pathway resembles the direct pathway, but this time the intact allogeneic HLA molecules are on the surface of the recipient APCs after transfer via exosomes or extracellular vesicles[112,113]. In contrast, the indirect pathway involves recognition by the recipient's T cells of peptides derived from allogeneic HLA molecules and presented within self-HLA molecules[114,115].

Because the TCRs of ILTCs (MAIT, γδ T cells, and NKT) do not bind to MHC molecules, there is no evidence in the literature that these cell subsets can participate in allorecognition through any of the 3 pathways described above. However, there are other (TCR-independent) mechanisms by which ILCs/ILTCs may participate in allorecognition.

ILC3s support primary and memory adaptive immune responses

LTi are crucial for the development of secondary lymhoid organs, which are essential for building up an alloimmune response. Splenectomized, aly-/- mice, which lack all secondary lymphoid organs, are unable to mount an adaptive response after allogeneic heart transplantation, and "ignore" the graft that is therefore not rejected[116]. It remains unclear if LTi also participate in chronic rejection-associated lymphoid neogenesis and the formation of intragraft tertiary lymphoid structures[117–119].

A study has reported that following stimulation with IL-1β, ILC3s upregulate MHC-II and costimulation molecules (CD40, CD80, CD86) and that they are capable of processing protein antigens and eliciting a CD4 T response *in vitro*. In vivo, the cognate interaction between ILC3s and CD4 T leads to proliferation of the latter while its blockade inhibits thymo-dependent B responses[120]. However, the fact that ILCs may present antigens is not universally accepted and needs to be confirmed.

Finally, LTi that express high levels of TNF ligands (OX40L and CD30L), are important for the survival of CD4+ memory T lymphocytes in the secondary lymphoid organs[121] and for secondary antibody responses[122].

The elusive role of γδ T cells in alloimmune responses

Studies published over a decade ago have reported that γδ T cells can interact with B cells, promote the formation of germinal centers, and induce the production of switched antibodies of IgE and IgG1 isotypes in mouse models[123–125]. The Vγ9+Vδ2+ cells express CXCR5, which allows their positioning in the B cell areas of the secondary lymphoid organs. Vγ9+Vδ2+ cells have been shown to support the production of switched antibodies, in a way that is dependent on CD40L, ICOS, and interleukins 4 and 10[126]. Beyond their "T follicular help (Tfh)-like" function, γδ T cells could also act indirectly by inducing Tfh differentiation through: i) the secretion of Wnt agonists, which allow the Tfh program to be initiated under the control of Ascl2[127], and ii) the presentation of antigenic peptides within MHC-II[128]. Collectively, this literature supports the idea that recipient γδ T cells could participate in humoral alloimmune response. However, in a recent set of experiments conducted in a murine model of heart transplantation, our group failed to show any defects in donor specific antibody (DSA) generation in recipient mice devoid of γδ T cells or any generation of DSA in recipient mice with only γδ T cells. Other evidence that γδ T cells are incapable of allorecognition comes from the observation that they cannot induce graft versus host disease (GVHD) in mice[129].

Role of ILC and ILTCs in tolerance to allogeneic transplants

NK cells control the direct allorecognition pathway

Beilke et al. have reported that tolerance to allogeneic pancreatic islets in mice is dependent on the recipient's NK cells[130]. Other studies using a skin graft model have

proven that NK-cell-dependent tolerance results from the destruction of the donor's passenger APCs contained in the graft[131], which in turn prevents the priming of the recipient's T lymphocytes through the direct pathway[132,133]. The same mechanism allows the recipient's NK cells to destroy donor's passenger CD4+ T cells, and thereby block the activation of the recipient's B cells and the magnitude of the humoral response[134]. In all these studies, donor mice were of H-2^d genetic background while recipient mice were H-2^b and it was discovered that the H-$2D^d$ molecules expressed on the surface of the graft cells constituted a ligand for the NKaR Ly49D[133,135]. Of note, the recipient's NK cells could use the same mechanism to also destroy the syngeneic APCs involved in the semi-direct pathway (after capture of the donor's intact MHC-I).

Nkp44 is another activating immunoglobulin-like receptor[136] expressed by activated NK lymphocytes (and a small number of T lymphocytes γδ[136,137]. Niehrs et al. recently reported that Nkp44 binds to HLA-DP*0401[138,139], a molecule highly expressed by activated APCs. While no studies have been conducted so far to validate this hypothesis, it is tempting to speculate that Nkp44 could suppress the direct allorecognition pathway in humans, as Ly49D does in mice.

NKT and tolerance

Although NKT deficiency does not modify the prognosis after allogeneic heart transplantation, this subset of ILLC seem to participate in the tolerance induced by the LFA-1 or CD28/B7 blockade. Indeed, tolerance to an allogeneic heart transplant induced by such immunosuppressive protocols is lost in the absence of NKT cells and restored after transfer of these cells in NKT KO mice[140]. Furthermore, in tolerant mice, NKT lymphocytes produce more IL-10, and this production is associated with the induction of IL-10-producing regulatory DCs and CD4+ T cells[141]. Other teams have reported the involvement of NKT cells in islet graft tolerance but suggest that their role

depends on TGFβ in this context[142]. How NKT cells are activated and acquire their tolerogenic functions after transplantation remains unknown.

γδ T cells and tolerance to liver allograft

Alterations of the γδ T lymphocyte compartment after viral (in particular CMV) infections have been frequently observed in liver and kidney transplant patients[143,144]. Interestingly, CMV infections have been associated with decreased reactivity of allospecific T-lymphocytes and a lower incidence of late cell rejection after liver transplantation. The virus-induced remodeling of the γδ compartment favors the Vδ1 subset[145], a population identified in the signature of tolerant liver transplant patients[146,147], but absent in rejected organs[148]. Some authors have proposed using the Vδ1 signature as a diagnostic test of operational tolerance, a phenomenon commonly observed after liver transplantation[147]. Whether the Vδ1 T lymphocytes are only a marker or are also players (and through which mechanisms) of this tolerance remain to be clarified.

MAIT cells prevent graft-versus-host disease of the gut

Colonic MAIT cells locally suppress the presentation of alloantigens by a donor's DCs, thus limiting the expansion of effector alloreactive T and GVHD lesions in the gut[149]. This data suggests that further exploration of the role of MAIT cells in intestinal transplantationis needed.

ILCs and ILTCs influence on the mechanisms of graft destruction

Missing self-induced NK cell activation and chronic vascular rejection

In contrast to the adaptive alloimmune response, in which the priming (i.e. allorecognition, see above) and effector phases are separated, both in time and space,

innate immune cells sense the allogeneic non-self and react against it in the same movement.

More than a decade ago, Uehara et al demonstrated that chronic vascular rejection lesions develop in cardiac allografts transplanted from parental to unmanipulated F1 hybrid mice, a transplant system that lacks specific anti-donor T cell reactivity but retains anti-donor NK cell responses[150]. Van Bergen et al reported that the existence of mismatches between NKiR of the recipient and MHC-I of the graft correlated with reduced graft survival after an HLA-A, B and DR compatible kidney transplantation[151]. A recent translational study recently shed light on the molecular mechanisms underlying these observations. Recipient's NK cells are equipped with surface NKiR, which have MHC-I molecules as ligands. Because the endothelium of a transplanted organ expresses the donor's MHC-I molecules, certain donor/recipient pairs create a "missing self" situation, in which the endothelial cells of the graft are unable to deliver HLA I-mediated inhibitory signals to recipient circulating NK cells. If the proportion of NK cells expressing the educated NKiR in the recipient is sufficient and following priming (by viral infection or IRI for instance), the missing-self activates NK cells, which in turn promote microvascular inflammation leading to reduced survival of the graft[152,153]. This new type of "innate" chronic vascular rejection could account for a significant (30 to 50%) fraction of patients with microvascular inflammation on graft biopsy but no detectable DSA in circulation[152]. This is of importance because, in contrast with chronic (i.e. complement-independent) antibody-mediated rejection (AMR), for which no efficient therapy is available, the mTOR inhibitor rapamycin can prevent the development of "innate" chronic vascular rejection in a murine model[152]. It is of note that an important proportion of γδ T cells also express NKiR[154,155] and could thereby also participate in the response to missing-self situations.

If a defect in inhibitory signals is sufficient to activate the NK cells within the microvascularisation of the graft, it is tempting to speculate that an excess of activation signals could do the same. MICA is a ligand of the NKaR NKG2D. MICA molecules are constitutively expressed on the surface of endothelial cells[156,157]. This highly polymorphic protein[158,159] can induce a humoral adaptive alloimmune response resulting in the production of anti-MICA DSA[157,160,161]. Interestingly, MICA polymorphisms also affect its binding to NKG2D. In particular, the MICA-129/Met polymorphism induces stronger NKG2D signaling[162]. It is therefore plausible that when the NK cells of a MICA-129/Met-negative recipient encounter MICA molecules on the surface of graft from a MICA-129/Met-positive donor, recipient's NK cells get activated, leading to "innate" chronic vascular rejection without "missing self". Along the same line, Nkp44 is another NKaR that binds to HLA-DP*0401. Endothelial cells of the grafts express MHC-II molecules upon exposure to inflammatory cytokines[163]. It is therefore conceivable that the endothelium of the grafts from an HLA-DP*0401-positive donor could trigger activation of the recipient’s NK cells.

FcγR-expressing ILCs and ILTCs contribute to chronic AMR pathophysiology

Antibody-mediated rejection associated with acute dysfunction of the graft is due to activation of the classical complement pathway[164]. Lower titers of DSA fail to activate the complement but are still associated with reduced graft survival due to (complement-independent) chronic AMR[165].

Colvin’s group was the first to demonstrate the crucial role of NK cells in the pathophysiology of chronic AMR. Using a murine model in which an allogeneic heart was transplanted to RAG-KO recipients (devoid of T and B cells) that were passively transfused with DSA, they showed that the recipient's NK cells infiltrate the intima of the arteries of chronically rejected grafts[166] and that NK cell depletion abrogated the

development of vascular lesions[166–168]. DSA bound to the surface of graft endothelium, indeed recruit NK cells through their crystallizable fragment, which binds to the CD16 (FcγRIII) receptor [169,170] and triggers ADCC (Antibody-dependent cellular cytotoxicity) and microvascular inflammation lesions[167,171,172].

This experimental data was then confirmed in clinical studies. The humoral rejection biopsies of kidney grafts were enriched with specific transcripts of NK lymphocytes[173,174] as a result of CD16-dependent signals[175].

Finally, our group recently demonstrated that the two mechanisms by which NK cells can get activated by an allogeneic transplant (i.e. missing self and ADCC) can synergize to accelerate kidney graft loss in patients with low DSA titers[176].

It has been shown that CMV infection in renal transplant recipients induces the expansion of a subpopulation of Vδ2-negativeT cells, which represents a population as large as NK cells among CD16-expressing PBMCs[177] and maintain over time[144]. Interestingly, CD16-expressing Vδ2-negativeT cells can perform ADCC in vitro against allogeneic target cells coated with DSA. The involvement of Vδ2-negativeT cells in AMR pathophysiology is further suggested *in vivo* by: i) the observation of Vδ2-negativeT cells in contact with microvascular cells in AMR biopsies of kidney grafts, and ii) the fact that their frequency in circulation is inversely correlated with graft function in patients with DSA[178].

Some authors have proposed that γδ T cells could also promote graft destruction by providing IL-17, which accelerates allograft rejection by locally increasing inflammation and preventing the expansion of regulatory T cells[179,180]. This hypothesis is supported by data from murine heart transplantation models but remains to be confirmed in humans.

I(L)LCs-mediated graft protection

As suggested above, ILCs play a crucial role in the homeostasis of mucosal organs, particularly the lung and intestine, and participate in the repair of damaged epithelia. For instance, influenza virus triggers an IL-33-dependent response in the lungs leading in ILCs to the upregulation of genes involved in tissue repair, including amphiregulin, an essential mediator of functional recovery of the lungs after infection[40]. If intestine damage is present, ILC3 synthesize IL-22 to promote regeneration of the epithelium by intestinal stem cells[80]. They also contribute to the maintenance of intestinal homeostasis via the secretion of IL-22, IL-17 and GM-CSF, which participate in the maintenance of the equilibrium between anti-microbial defense and tolerance of commensal bacteria[181–184].

In the field of transplantation, emerging data seems to confirm the protective role of ILCs. In a murine model of lung transplantation, it has been reported that the production of IL-22 by intragraft ILC3 (and γδ T cells) allows for recruiting the recipient's B lymphocytes within the BALT and thereby promotes long-term lung graft tolerance[185,186]. In accordance with this concept, a recent clinical study has established a correlation between lung graft dysfunction and a decrease in ILC2 in lung tissue[187]. In addition, NK and NKT cells could also protect allografts. Chronic lung rejection is associated with a decrease in the expression, by NK and NKT cells, of anti-inflammatory molecules, which (if increased by drug treatments) could potentially improve graft survival [188,189].

Donor chimerism is long lasting in the ILC compartment of intestinal transplant[190,191] and whether they originate from the recipient or the donor, ILC3 seem to be associated with the clinical outcome. A first study has indeed reported that early repopulation of intestinal grafts by IL-22- synthesizing ILC3 is associated with a better outcome[192],

while a second work has shown that intestinal rejection is associated with a local decrease in ILC3 and IL-22 secretion[193].

ILCs and ILTCs protect transplant recipients of the side effects of therapeutic immunosuppression

Prevention of rejection in transplant recipients relies on non-specific life-long immunosuppression, which increases the risk for infection and neoplasia.

Most immunosuppressive regimens include an induction followed by maintenance with a combination of drugs. Depleting agents used for induction (thymoglobulin, alemtuzumab…etc) are antibodies; they have limited ability to diffuse outside the circulation[194], which suggests that tissue-resident cell subsets are relatively preserved. Maintenance immunosuppression principally relies on calcineurin-inhibitors that target the signal 1 of activation, downstream from the T- or B-CR of lymphocytes. Classical immunosuppressive strategies could thus spare ILCs (and to a certain extend ILTCs, which can be activated through TCR-independent pathways)[195,196]. This specificity, together with the fact that ILCs or ILTCs have important roles in first line defense against infections and tumors, suggests that these cells could play an important protective role in transplant recipients.

Roles of ILCs in infections and cancers

Gut ILCs have critical roles in cytokine-mediated regulation of intestinal epithelial cell barrier integrity. ILCs that express major histocompatibility complex class II, and can process and present antigen, also regulate CD4+ T-cell and limit pathological adaptive immune cell responses to commensal bacteria[182].

ILC1 have been implicated in the response against two classical pathogens following transplantation: CMV[31] and *Toxoplasma gondii*[197]. ILC1 also play a critical role for the

maintenance of lung airway epithelial integrity, especially following infection with influenza virus[40], a role they share with iNKT cells[198].

The role of NK cells and other ILCs in tumors has been extensively reviewed elsewhere[199,200]. We will here only underlie the important *graft versus leukemia* effect of NK cells. The donor NK cell alloreactivity is indeed effective in mismatched hematopoietic transplants in protecting the recipient[201]. Early NK cell recovery is associated with better cancer-free survival after autologous hematopoietic stem cell transplantation[202]. In solid organ transplants, dysfunction of NK cells (decreased expression of NKp46, decreased number of IFNγ-producing NK cells) is associated with post-transplant malignancy[203,204].

NK cells function also predicts severe infection in kidney transplant recipients[205]. Interestingly, a more specific role for NK cells in anti-CMV response was recently highlighted. NK cells exhibit adaptive immune features after CMV infection in mouse (proliferation capacity, memory phenotype and efficacy of adoptive transfer[206]). Cytomegalovirus reactivation after allogeneic transplantation promotes a long-lasting increase in adaptive NKG2C+ NK cells with more potent functions[207]. Human CMV also imprints KIR repertoire towards activating KIR with the expansion of a unique NKG2C+CD57+ subset of NK cells[208,209]. These CMV NKG2C+ NK cells were enriched in bronchoalveolar lavages of lung allograft and inversely correlated with CMV blood titers[210]. This subset may therefore represent a signature associated with reduced incidence of post-transplantation symptomatic CMV[211].

Roles of ILTCs in infections and cancers

MAIT cells are involved in the maintenance of gut integrity and in the response to a large panel of bacteria[212,213], including the very common Escherichia Coli that induces pyelonephritis ; and viruses[214,215].

The role of Vδ2-negative γδ T cells in CMV response was first demonstrated in immunocompromised solid organ transplant recipients[144,216]. This seminal observation has since been extended to other settings of αβ T cell deficiencies: immaturity[217], congenital immunodeficiency[218], bone marrow transplantation[219] and finally, also confirmed in healthy blood donors[220].

Anti-CMV Vδ2-negative γδ T cells display a late differentiated TEMRA (CD27-CD28-CD45RA+CCDR7-CD62L-) and activated (CD69+HLA-DR+) phenotype, cytotoxic ability (perforin+ granzymeB+) and expression of NKRs (CD16+, NKG2D+, CD94/NKG2C/A+). CMV drives a presumed antigen-driven clonal selection with a repertoire restriction of the γδ TCR (CDR3 restriction for the Vδ chains). Longitudinal surveillance of non Vγ9+Vδ2+ γδ T cells in kidney transplant recipients may predict CMV infection resolution and antiviral drug resistance[221]. Notably, γδ T lines/clones from CMV-infected patients kill both CMV-infected cells and several solid tumor cell lines in a TCR-dependent fashion[222]. In agreement with this TCR-dependent cross-reactivity, an association between a high percentage of CMV-responsive γδ T lymphocytes in blood and a reduced cancer risk was observed in kidney recipients[223].

Conclusion

Innate immune effectors are finally getting attention from transplant immunologists and their many roles are starting to be recognized beyond the initial ischemia/reperfusion phase. Like their myeloid counterparts, which have been shown to be capable of allorecognition, innate lymphoid cells (in particular NK cells through missing-self) can detect allogeneic non-self. Furthermore, convincing (direct or indirect) evidence suggests that almost all known ILC and ILLC subsets can participate in rejection by accelerating or dampening graft destruction depending on the organ and the context. Finally, it should not be forgotten that ILCs and ILTCs contribute to the first line of defense against pathogens and cancers. Because these subsets might be less affected by immunosuppressive drugs, ILCs and ILTCs could play crucial roles in the protection of transplant recipients against these life-threatening complications (Figure 4).

Given the complexity of this field, intense efforts are still required to elucidate the exact role of each of these subsets in transplant immunology.

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Figure legends

Figure 1. A simplified classification for lymphoid cells

Abbreviations are: ILC, Innate lymphoid cell; NK, natural killer; LTi, lymphoid tissue inducer; MAIT, Mucosal associated invariant T; NKT, Natural killer T; TCR, T cell receptor; MZ, marginal zone.

Figure 2. Characteristics and functions of innate lymphoid cells

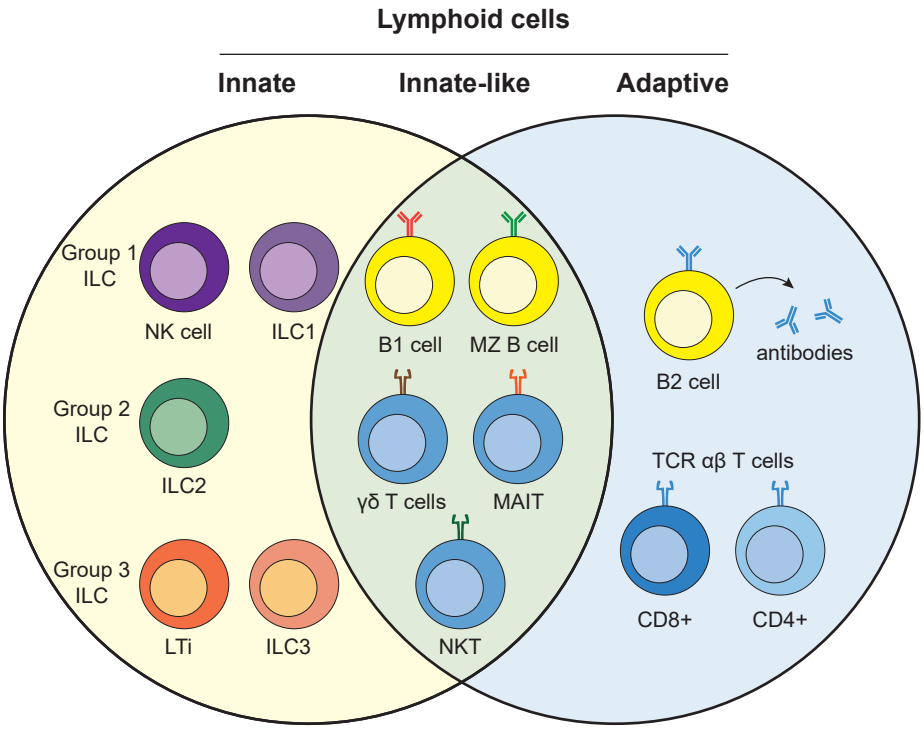
Abbreviations: ILC, Innate lymphoid cell; NK, natural killer; LTi, lymphoid tissue inducer; IFN, interferon; IL, interleukin.

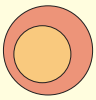
Figure 3. Characteristics and functions of innate-like T cells

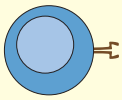
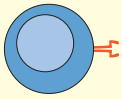
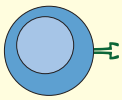
Abbreviations: MAIT, Mucosal associated invariant T; NKT, Natural killer T; TCR, T cell receptor; IFN, interferon; IL, interleukin; Ag, antigen; αGalCer, α-galactosylceramide; CMV, cytomegalovirus.

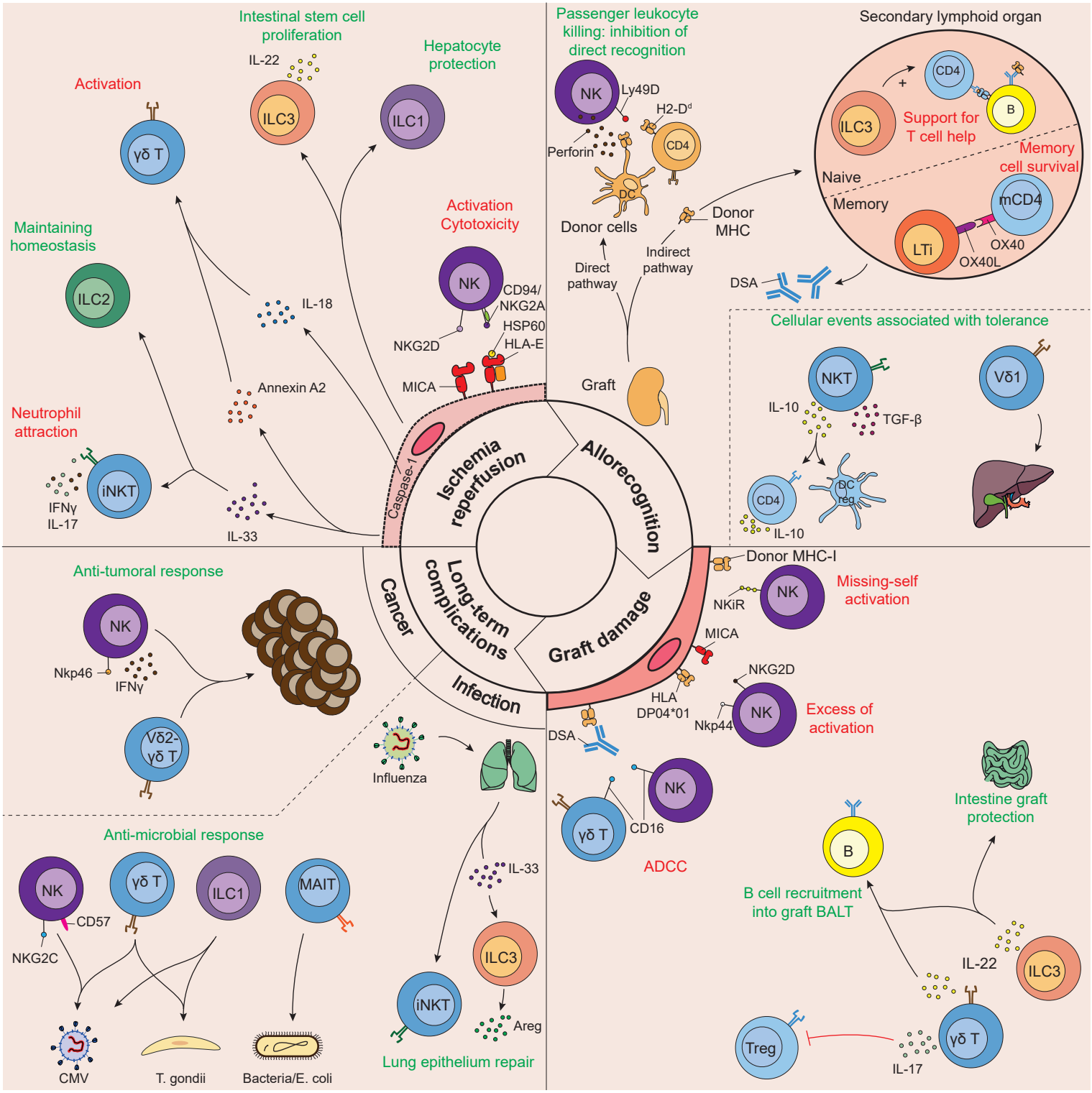
Figure 4. Graphical summary of the possible roles of innate (and innate-like) lymphoid cells in transplantation

Abbreviations are: ILC, Innate lymphoid cell; NK, natural killer; LTi, lymphoid tissue inducer; MAIT, Mucosal associated invariant T; NKT, Natural killer T; TCR, T cell receptor; IFN, interferon; IL, interleukin; MHC, major histocompatibility complex; MICA, MHC-I polypeptide–related sequence A; HLA, human leukocyte antigen; DSA, donor specific antibody; CMV, cytomegalovirus ; TGF, transforming growth factor; ADCC, antibody-dependent cellular cytotoxicity; Areg, Amphiregulin; BALT, bronchus-associated lymphoid tissue.

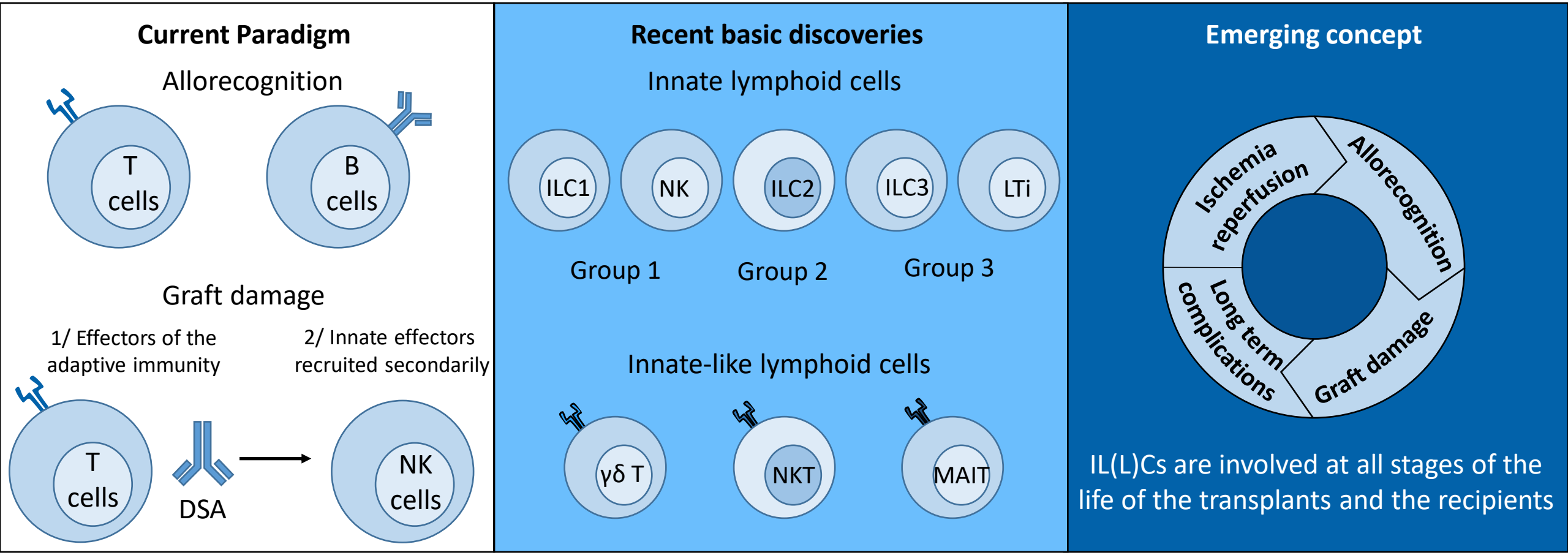

Lymphoid cells
Innate
Innate-like
Adaptive
Group 1 ILC
NK cell
ILC1
Group 2 ILC
ILC2
Group 3 ILC
LTi
ILC3
B1 cell
MZ B cell
γδ T cells
MAIT
NKT
B2 cell
antibodies
TCR αβ T cells
CD8+
CD4+

	ILC	Transcription factors	Effectors molecules	Function	Disease association
Group 1	 ILC1	T-bet	IFNγ	Intracellular pathogens	
	 NK cell	T-bet Eomes	Perforin Granzyme IFNγ	Immunity to viruses and intracellular pathogens Tumor surveillance	Viral infection Cancer
Group 2	 ILC2	GATA3	IL-5 IL-13 Amphiregulin	Immunity to helminths	Allergy Asthma
Group 3	 LTi	RORγt	IL-17A IL-22 Lymphotoxin	Lymphoid tissue development Immunity to extracellular bacteria	
	 ILC3	RORγt	IL-17 IL-22	Homeostasis of epithelia Immunity to extracellular bacteria	Inflammatory bowel disease

ILLC	TCR specificity	Effectors molecules	Function	Disease association
 γδ T cells	*Vγ9+Vδ2+:* Phospho-Ag/Butyrophilin *Non Vγ9+Vδ2+:* Stress-induced Ag	Perforin Granzyme IFNγ IL-17	Lymphoid stress surveillance	*Vγ9+Vδ2+:* Plasmodium/Toxoplasma/ Gram+ bacteria infections Cancer *Non Vγ9+Vδ2+:* CMV infection Cancer
 MAIT	Riboflavin metabolites bound to MR1	Perforin Granzyme IFNγ IL-17	Tissue homeostatis Interface immunity	Infections Inflammatory disease Cancer
 NKT	αGalCer (or glyco-/phospholipid Ag) bound to CD1d	Perforin Granzyme IFNγ IL-17 IL-4	Immune response regulation	Cancer Preeclampsia


Intestinal stem cell proliferation
IL-22
ILC3
Hepatocyte protection
ILC1
Activation
γδ T
Maintaining homeostasis
ILC2
IL-18
Activation
Cytotoxicity
NK
CD94/
NKG2A
HSP60
HLA-E
NKG2D
MICA
Annexin A2
Neutrophil attraction
iNKT
IFNγ
IL-17
IL-33
Caspase-1
Ischemia reperfusion
Allorecognition
Long-term complications
Cancer
Graft damage
Infection
Passenger leukocyte killing: inhibition of direct recognition
NK
Ly49D
H2-D^d
Perforin
CD4
DC
Donor cells
Donor MHC
Direct pathway
Indirect pathway
Graft
Secondary lymphoid organ
CD4
+
B
ILC3
Support for T cell help
Memory cell survival
Naive
Memory
mCD4
LTi
OX40
OX40L
DSA
Cellular events associated with tolerance
NKT
IL-10
TGF-β
Vδ1
CD4
DC reg
IL-10
Anti-tumoral response
NK
Nkp46
IFNγ
Vδ2-γδ T
Donor MHC-I
NKiR
NK
Missing-self activation
MICA
NKG2D
HLA DP04*01
NK
Nkp44
Excess of activation
DSA
Influenza
γδ T
CD16
NK
ADCC
Anti-microbial response
NK
CD57
NKG2C
γδ T
ILC1
MAIT
CMV
T. gondii
Bacteria/E. coli
IL-33
ILC3
iNKT
Areg
Lung epithelium repair
Intestine graft protection
B
B cell recruitment into graft BALT
IL-22
ILC3
Treg
γδ T
IL-17

Innate (and innate-like) lymphoid cells: emerging immune subsets with multiple roles along transplant life



Charmetant, Bachelet et al. *Transplantation*. 2021